



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2020-N-1228]

### Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Study of Multiple Indications in Direct-to-Consumer Television Advertisements

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

**DATES:** Submit written comments (including recommendations) on the collection of information by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

**ADDRESSES:** To ensure that comments on the information collection are received, OMB recommends that written comments be submitted to <https://www.reginfo.gov/public/do/PRAMain>. Find this particular information collection by selecting "Currently under Review--Open for Public Comments" or by using the search function. The title of this information collection is "Study of Multiple Indications in Direct-to-Consumer Television Advertisements." Also include the FDA docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Ila S. Mizrachi, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-7726, [PRASStaff@fda.hhs.gov](mailto:PRASStaff@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:** In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Study of Multiple Indications in Direct-to-Consumer Television Advertisements

OMB Control Number 0910-NEW

Section 1701(a)(4) of the Public Health Service Act (42 U.S.C. 300u(a)(4)) authorizes the FDA to conduct research relating to health information. Section 1003(d)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 393(d)(2)(C)) authorizes FDA to conduct research relating to drugs and other FDA regulated products in carrying out the provisions of the FD&C Act.

The Office of Prescription Drug Promotion's (OPDP) mission is to protect the public health by helping to ensure that prescription drug promotion is truthful, balanced, and accurately communicated. OPDP's research program provides scientific evidence to help ensure that our policies related to prescription drug promotion will have the greatest benefit to public health.

Toward that end, we have consistently conducted research to evaluate the aspects of prescription drug promotion that are most central to our mission, focusing in particular on three main topic areas: (1) advertising features, including content and format; (2) target populations; and (3) research quality. Through the evaluation of advertising features, we assess how elements such as graphics, format, and disease and product characteristics impact the communication and understanding of prescription drug risks and benefits. Focusing on target populations allows us to evaluate how understanding of prescription drug risks and benefits may vary as a function of audience, and our focus on research quality aims at maximizing the quality of research data through analytical methodology development and investigation of sampling and response issues. This study will inform the first topic area, advertising features, including content and format.

Because we recognize the strength of data and the confidence in the robust nature of the findings is improved through the results of multiple converging studies, we continue to develop evidence to inform our thinking. We evaluate the results from our studies within the broader

context of research and findings from other sources, and this larger body of knowledge collectively informs our policies as well as our research program. Our research is documented on our homepage, which can be found at: <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp-research>. The website includes links to the latest *Federal Register* notices and peer-reviewed publications produced by our office. The website maintains information on studies we have conducted, dating back to a direct-to-consumer (DTC) survey conducted in 1999.

A number of prescription drugs are approved for multiple indications. These indications can be similar in certain respects (e.g., diabetic peripheral neuropathy and fibromyalgia, which are both conditions that manifest in pain) or very different from one another (e.g., diabetic peripheral neuropathy and generalized anxiety disorder). If a drug is approved for multiple indications, sponsors choose whether to promote only one of those indications in DTC television advertising, or multiple indications in the same television advertisement. We are unaware of any quantitative research that addresses how presenting multiple indications in one advertisement affects consumers' processing of drug information. Some research suggests that presenting more than one indication in a television advertisement, regardless of the similarity of the indications, may increase the cognitive load on consumers, thus decreasing their understanding of the drug's indications (Refs. 1-3).

When more than one indication is presented, the similarity or dissimilarity of the indications may affect participants' ability to remember and understand the indications. If this is the case, it is not clear whether similarity would have a positive or negative effect in the multimodal context of a television advertisement (e.g., Refs. 4 and 5).

This study will provide preliminary information on whether consumers face challenges when multiple indications are promoted in a single television advertisement. The study also will explore whether similarity of the indications affects participants' likelihood to recall and understand the indications, and whether its effect would be positive or negative.

We propose to test three types of fictional DTC television advertisements--one that promotes a single indication, one that promotes an indication plus a similar indication, and one that promotes an indication plus a dissimilar indication--in two different medical conditions (table 1).

Table 1.--Study Design:  $1 \times 3$  Factorial Experiment Repeated in Two Medical Conditions

	Indication 1	Indication 1 Plus a Similar Indication	Indication 1 Plus a Dissimilar Indication
Study 1: Diabetic peripheral neuropathy (DPN)	DPN	DPN + fibromyalgia	DPN + generalized anxiety disorder
Study 2: Rheumatoid arthritis (RA)	RA	RA + psoriatic arthritis	RA + ulcerative colitis

We plan to conduct two pretests (one for each main study) and two main studies not longer than 20 minutes, administered via internet panel, to test the experimental manipulations and pilot the main study procedures. Participants will be randomly assigned to view one study advertisement and then complete a questionnaire that assesses recall and comprehension of the drug's benefits and risks, benefit and risk perceptions, attitudes, and behavioral intentions. We will also measure covariates such as demographics and health literacy. Taking into account prior research, it is our hypothesis that participants will be more likely to correctly recall and understand the first indication when it is presented alone, compared with when it is presented with a second (similar or dissimilar) indication. We will explore whether similarity of the indications affects participants' likelihood to recall and understand the indications. We will also explore the effects of the indication presentation on benefit and risk perceptions, attitudes toward the drug and the indication information, and intentions to look for more information and ask a doctor about the drug.

For all phases of this research, we will recruit adult volunteers 18 years of age or older. For Pretest 1 and Study 1, we will recruit participants who self-report being diagnosed with diabetes ( $N = 60$  in Pretest 1 and  $N = 402$  in Study 1). For Pretest 2 and Study 2, we will recruit participants who self-report being diagnosed with rheumatoid arthritis ( $N = 60$  in Pretest 2 and  $N = 402$  in Study 2). We will exclude individuals who work for the Department of Health and

Human Services or work in the healthcare, marketing, or pharmaceutical industries. We will also exclude pretest participants from the main studies, and participants will not be able to participate in both Studies 1 and 2. With these sample sizes, we will have sufficient power to detect small-sized effects in Studies 1 and 2. For the burden estimate, we include an additional 10% over our target number of valid completes to account for some overage.

In the *Federal Register* of July 6, 2020 (85 FR 40296), FDA published a 60-day notice requesting public comment on the proposed collection of information. FDA received four comments that were PRA-related.

Within the four submissions, FDA received multiple comments that the Agency has addressed below. For brevity, some public comments are paraphrased and therefore may not reflect the exact language used by the commenter. We assure commenters that the entirety of their comments was considered even if not fully captured by our paraphrasing in this document.

(Comment) One comment suggested several ideas for other study designs, including: (1) studying consumer reactions to actual advertisement campaigns; (2) studying consumer reactions to watching a DTC television advertisement and then viewing a related website; and (3) studying advertisements for multiple indications with different risk profiles. Another comment suggested another study idea: studying a drug with multiple indications for the same disease.

(Response) We appreciate these alternate study ideas. As this is the first study on this topic, we acknowledge our study cannot answer every research question. We believe these alternate study ideas could be candidates for future research, and we encourage stakeholders to conduct research in this area.

(Comment) One comment recommended using Crohn's or ulcerative colitis rather than leukemia as the dissimilar indication in Study 2 to avoid confusion with adverse effects of common RA medications.

(Response) Based on this comment, we plan to use ulcerative colitis rather than leukemia as the dissimilar indication in Study 2.

(Comment) Three comments noted that care should be taken to reduce confounding variables in the study stimuli in terms of length, order and presentation of indications, background and actor profiles, advertisement quality, and audio and visual effects.

(Response) We can confirm that care has been taken to ensure that we do not have any unintentional confounds across the study conditions. The advertisements use the same actors, scenes, audio and visual effects and all other design and content features to ensure that all elements are consistent across experimental conditions. We also used the same setting, actors, and advertisement concept across Study 1 and Study 2 to minimize differences across the two studies. The only aspect that will change is the manipulated content (i.e., script and superimposed text relaying the indications).

(Comment) One comment requested that we clarify how we are defining similar versus dissimilar indications.

(Response) The similar indications have similar clinical manifestations: in Study 1, nerve-related pain for diabetic peripheral neuropathy and fibromyalgia, and in Study 2, joint pain for rheumatoid arthritis and psoriatic arthritis. The dissimilar indications have dissimilar clinical manifestations: in Study 1, nerve-related pain for diabetic peripheral neuropathy and anxiety for generalized anxiety disorder, and in Study 2, joint pain for rheumatoid arthritis and abdominal pain and diarrhea for ulcerative colitis.

(Comment) One comment recommended stratification across conditions for demographics and several health characteristics.

(Response) Typically, stratified randomization is used if there are prognostic variables that correlate with outcome measures and researchers are concerned about such factors not being evenly distributed across groups (Ref. 6). We have no reason to expect that the aforementioned factors would have a strong association with the outcome measures, nor do we have reason to believe that we will not achieve adequate balance of prognostic variables given the large sample size proposed for this study (Ref. 6). Random assignment will help to produce groups which are,

on average, probabilistically similar to each other. Because randomization eliminates most other sources of systematic variation, we can be reasonably confident that any effect that is found is the result of the intervention and not some preexisting differences between the groups (Ref. 7). However, we have included questions about demographics and health characteristics, which will enable us to assess their association with our outcomes and statistically control for them if necessary.

(Comment) One comment noted that the sample size per cell should be at least 75 participants.

(Response) We conducted power analyses to determine sample size. We plan to have 134 participants per cell in each study, for a total of 402 participants per study.

(Comment) One comment noted that recruiting participants with only the primary indication could bias results because participants will be more familiar with their own medical condition. Instead, it suggested that for each study condition we recruit a sample that matches that study condition (e.g., recruiting participants with diabetic peripheral neuropathy or fibromyalgia for the second study condition in Study 1).

(Response) We agree that participants may know more about their own medical condition than the other medical conditions advertised. However, we believe the alternate design offered in the comment would make results difficult to interpret as it would be unclear whether differences were due to the advertisement manipulations or to the different samples. Instead, we plan to keep the original design. We do not plan to compare participants' recall, recognition, or comprehension of the primary indication to the second indication (which may lead to the bias noted in the comment). Rather, we plan to compare understanding across the experimental conditions. For instance, we are testing the hypothesis that participants (with diabetes in Study 1 and rheumatoid arthritis in Study 2) who see the first indication alone will be more likely to recall, recognize, and comprehend the first indication compared with participants (with diabetes in Study 1 and rheumatoid arthritis in Study 2) who see the first indication and a second (similar

or dissimilar) indication. As another example, we would expect that recall, recognition, and comprehension of the second indication would be higher when the second indication is mentioned in the advertisement compared with when it is not (e.g., participants are more likely to know the drug is also indicated for fibromyalgia when the advertisement mentions the fibromyalgia indication). We will measure participants' familiarity with treatments for each medical condition and assess whether they have been diagnosed with each medical condition. We can use these variables to explore differences among participants. A future study could examine how individuals suffering from fibromyalgia or generalized anxiety, or from psoriatic arthritis or ulcerative colitis (which are secondary indications in the current study) may interpret these advertisements.

(Comment) One comment suggested recruiting participants with diabetic peripheral neuropathy specifically rather than diabetes in Study 1, while another comment noted that diabetic peripheral neuropathy is underdiagnosed and therefore may present recruitment challenges.

(Response) We plan to retain the diabetes sample for Study 1 to aid recruitment. We will ask participants if they experience diabetes-related pain and whether they have been diagnosed with diabetic peripheral neuropathy.

(Comment) One comment noted concern about the chosen indications because medical conditions can differ from one another in several ways (e.g., prevalence, treatment options) and suggested considering public awareness of the medical conditions.

(Response) We agree that medical conditions vary; this is unavoidable in a study of this kind. To account for this, we plan to conduct two studies using different medical conditions to determine whether the effects replicate across studies. We will measure participants' familiarity with treatments for the medical conditions in each study.

(Comment) One comment suggested asking participants if they were familiar with the fictitious drug and terminating participants who say yes.



(Response) It is unlikely that many participants will claim to be familiar with the fictional brand name. However, past research has noted the human tendency to falsely recognize content (Ref. 8). While theoretically interesting, the fact that people may falsely recognize our brand should not threaten the internal validity of the current study. Random assignment should guard against systematic differences among groups in terms of false recognition tendency. Nonetheless, we appreciate this concern and in response, we have added a question to the survey to measure familiarity with the brand, which we can then explore in auxiliary analyses, but we do not think participants with false brand familiarity should be removed from the study. Our study sample includes those with rheumatoid arthritis for one of the studies (a condition with lower prevalence in the United States, about 0.6 percent of the population). Excluding those with false recognition would impose additional burden on recruitment.

(Comment) One comment suggested that the questionnaire should include the statement "Based on the ad you just saw..." before each question.

(Response) We include this statement and similar language throughout the questionnaire.

(Comment) One comment suggested we measure unaided awareness of the indications, aided awareness of the indications, likelihood to go to the branded drug website to learn more about the drug, and likelihood to ask their doctor about the drug.

(Response) We measure unaided awareness of the indications (benefit recall) in Question 2, aided awareness of the indications (benefit recognition) in Question 3, and likelihood to look for more information about the drug and ask their doctor about the drug in Questions 16 and 17.

(Comment) One comment suggested deleting Questions 2 and 13 in favor of Questions 3 and 14 because these open-ended questions may be difficult for respondents to answer.

(Response) Questions 2 and 13 measure unaided recall of drug benefits and risks whereas Questions 3 and 14 measure recognition of drug benefits and risks. We agree that recall is more difficult than recognition. We plan to retain Questions 2 and 13 but will assess their utility in cognitive interviews and pretesting.

(Comment) One comment suggested using consistent scales on the questionnaire.

(Response) Most questionnaire items have true/false/don't know or yes/no/don't know response options. Some items are validated measures with Likert-type scales; for these, we have used the response options from the validated measures.

(Comment) Two comments suggested removing or revising questions 7-10 because participants do not have the medical expertise to say whether someone is a good candidate for a drug. Instead, the comments suggested asking whether the drug is appropriate for them.

(Response) These questions are intended to measure participants' comprehension of the indications as communicated in the advertisements. DTC advertisements can drive consumers to ask their doctors about a drug, so it is important to know whether the drug indication is accurately communicated to consumers. We used similar questions about being a "good candidate" in another study (OMB control number 0910-0885). In cognitive interviews, participants were able to answer the questions and they understood that the questions were asking about the drug information in the advertisement. We also tested language, such as whether it would be appropriate for the person to ask their doctor about the drug, but participants found this language to be wordy and unnecessary. We do not plan to change these questions at this time, but we will assess participants' ability to answer these questions in cognitive interviews and pretesting.

(Comment) Two comments suggested deleting or revising several items (Questions 16, 17, 21-24, 26, 27 in one comment, Questions 18-27 in the other) because responses to these items may be influenced by the particular stimuli used and by factors other than those being studied.

(Response) These items measure intentions, attitudes, and perceptions. We agree that several factors can influence these outcomes. However, random assignment to conditions allows us to determine whether the experimental manipulation is responsible for differences in these

outcomes across conditions. We will retain these items and assess their utility in cognitive interviews and pretesting.

(Comment) One comment suggested combining Questions 30 through 33 into one item and asking it at the beginning of the questionnaire.

(Response) We combined questions Q31 and Q32 into one item and moved the item to the screener.

(Comment) One comment suggested we ask participants if they have been diagnosed with the indicated medical conditions (diabetic neuropathy, fibromyalgia, etc.).

(Response) These questions are included on the questionnaire.

FDA estimates the burden of this collection of information as follows:

Table 2.--Estimated Annual Reporting Burden<sup>1</sup>

Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Respondents	Average Burden per Response	Total Hours
Pretest 1 and 2 screener	264	1	264	0.083 (5 minutes)	22
Pretest 1 and 2	132	1	132	0.333 (20 minutes)	44
Main Study 1 and 2 screener	1,770	1	1,770	0.083 (5 minutes)	147
Main Study 1 and 2	885	1	885	0.333 (20 minutes)	295
Total					508

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

## References

The following references are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; these are not available electronically at <https://www.regulations.gov> as these references are copyright protected. Some may be available at the website address, if listed. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Mayer, R. E. and R. Moreno (2003), "Nine Ways to Reduce Cognitive Load in Multimedia Learning." *Educational Psychologist*, 38(1), 43-52.

2. Mutlu-Bayraktar, D., V. Cosgun, and T. Altan (2019), "Cognitive Load in Multimedia Learning Environments: A Systematic Review." *Computers & Education*, 141, 103618.
3. Betts, K. R., V. Boudewyns, K. J. Aikin, C. Squire, et al. (2018), "Serious and Actionable Risks, Plus Disclosure: Investigating an Alternative Approach for Presenting Risk Information in Prescription Drug Television Advertisements." *Research in Social and Administrative Pharmacy*, 14(10), 951-963.
4. Jiang, Y. V., H. J. Lee, A. Asaad, and R. Remington (2016), "Similarity Effects in Visual Working Memory." *Psychonomic Bulletin & Review*, 23(2), 476-482.
5. Oberauer, K. and E. B. Lange (2008), "Interference in Verbal Working Memory: Distinguishing Similarity-Based Confusion, Feature Overwriting, and Feature Migration." *Journal of Memory and Language*, 58(3), 730-745.
6. Friedman, L. M., C. D. Furberg, and D. L. DeMets (1998), *Fundamentals of Clinical Trials*. New York, NY: Springer Science-Business Media, LLC.
7. Fisher, R. A. (1937), *The Design of Experiments*. Edinburgh, United Kingdom: Oliver and Boyd.
8. Southwell, B. G. and R. Langteau (2008), "Age, Memory Changes, and the Varying Utility of Recognition as a Media Effects Pathway". *Communication Methods and Measures*, 2, 100-114.

Dated: February 26, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.